Docket No. MACH2/CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Jehanne E. Souaya
Group	:	1634
Applicants	:	Bernard F. Mach et al.
Application No.	:	08/484,786 Confirmation No. 4894
Filed	:	June 7, 1995
For	:	DNA SEQUENCES CODING FOR THE DR β-CHAIN LOCUS OF THE HUMAN LYMPHOCYTE ANTIGEN COMPLEX AND POLYPEPTIDES, DIAGNOSTIC TYPING PROCESSES AND PRODUCTS RELATED THERETO

Hon. Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

SECOND DECLARATION OF JACK L. STROMINGER, M.D., D.Sc.
UNDER 37 C.F.R. § 1.132

I, Jack L. Strominger, M.D., D.Sc., declare and state as follows:

1. I make this declaration to supplement my March 28, 2002 declaration, filed on May 16, 2002, in connection with United States patent application no. 08/484,786 ("the '786 application").

2. I have read and considered the December 17, 2002 Office Action issued in the '786 application ("Office Action"). I have previously read and have now reviewed the '786 application,

in preparation of this declaration. I have also read and considered the "amended" claims 76-102 of the '786 application, which I am informed and believe to be submitted concurrently with the filing of this declaration, as part of the Amendment and Response to the December 17, 2002 Office Action (see Appendix to the Amendment and Response dated June 17, 2003).

3. I consider a person of skill in the art pertaining to the '786 application to be one skilled in the art of molecular immunology, and in particular, the field of HLA antigens, as well as the field of DNA hybridization, as of July 30, 1982 (a date not long after the beginning of the research involving HLA). Such a person would have a Ph.D. degree at that time and several years of relevant laboratory experience ("a person of skill in the art").

4. I make this declaration to address the concerns raised by the Examiner in the December 17, 2002 Office Action. More specifically, I make this declaration to address whether the claimed subject matter was described in the specification in such a way that a person of skill in the art as of July 30, 1982, would be able to make and/or use the invention. and to correct the Examiner's mis-interpretations regarding the uniformity of the conserved 39-45 amino acid region, taught by the '786 application.

5. The Examiner asserts that "the three sequences described in the specification [are] do not enable the skilled artisan to make or use the broad scope of the claimed invention without undue experimentation." (see page 15, lines 10-12 of the

December 17, 2002 Office Action) More specifically, the Examiner suggests that "the claims, as written, encompass polynucleotides and methods of using polynucleotides that vary substantially in length and in nucleotide composition." (see page 15, lines 5-7 of the December 17, 2002 Office Action). I respectfully disagree.

6. As stated in ¶¶ 15-16 of my declaration of May 16,2002, in pertinent part:

> "a person of skill in the art would have understood that the highly conserved DNA sequence and three polymorphic DNA sequences taught in the '786 application would also be useful for the identification and characterization of additional HLA-DR-β chain alleles." (¶ 15)
>
> Also,
>
> "DNA sequences encoding the identified polymorphic regions, or the specific DNA sequences for those regions, as identified in the '786 application for the HLA-DR-β-A, HLA-DR-β-B and HLA-DR-β-C alleles, all HLA-DR B1 alleles, could then be used to distinguish among different HLA-DR-β chain alleles. Thus, the polymorphic and conserved regions identified in the '786 application would have been extremely useful for hybridization-based HLA-DR typing." (¶ 16)

These statements are intended to demonstrate that, with the three polymorphic HLA-DR-β sequences and one conserved HLA-DR-β sequence, in hand, a person skilled in the art of HLA-DR-β typing would have understood that the designated "polymorphism" of the three disclosed HLA-DR-β DNA sequences provided the "common structural feature" by which the nucleotide sequences of additional polymorphic regions, namely 8-14, 26-32, and 72-78 of the HLA-DRB1 locus could be obtained.

7. As a person of skill in the art, as of July 30, 1982, it is my opinion that the polymorphic nature of the nucleotide sequence located at the 8-14, 26-32 and 72-78 regions of the HLA-DR-β allele would in fact provide useful structural information, for the identification and characterization of the nucleotide sequence located at the 8-14, 26-32 and 72-78 regions of other HLA-DR alleles.

8. The Examiner also contends that "the specification has not taught which positions within these regions can be changed and still be HLA-DR beta alleles and useful in a typing method". It is my opinion that this is not an accurate interpretation of the invention.

9. Specifically, it is my belief that a person of skill in the art, as of July 30, 1982, would recognize that "any" nucleotide change within the polymorphic regions that did not result in a gross change in the structure of the HLA-DR-β chain would be tolerated, and thus useful in a HLA typing method. By contrast only "minimal" nucleotide changes would be tolerated within the conserved region defined in the application. For example, of presently identified HLA-DR-β1, only 4 alleles vary at position 45 (G->R), 1 allele varies at position 39 (R->H), and 2 alleles vary at position 40 (F->Y). (see Exhibit K, submitted with my declaration dated May 16, 2002). All of these amino acid changes are the result of a "single" nucleotide change, located at

the end or adjacent to the end of the nucleotide sequence encoding the conserved region of the HLA-DR-β allele. Accordingly, there is no doubt in my mind that the nucleotides encoding the conserved region (e.g. amino acids 39-45), as described in the '786 application would in fact hybridize to "all" of the presently identified HLA-DR-β alleles. Additionally, of the seven alleles that contain a minor sequence variation, nearly all of the alleles represent rare subtypes (e.g., B1*0433; B1*0823 - last two numbers represent the subtype of each allele, high numbers are rare), and in some cases represent a single individual. Thus, these noted minor variation would represent a "very minor" faction of the entire population. It is my opinion that these minor variations would not diminish the importance and usefulness of the conserved region in the method and typing kits described in the '786 application.

10. More specifically, the Examiner asserts the specification "has not taught the variations within the DRB4 alleles which were later identified (for example within the conserved region of amino acids 39-45), such that the skilled artisan would have known at the time of filing that such variations would still be DR-beta alleles."

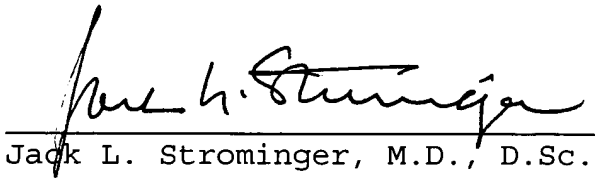
11. To address the Examiner's concern with respect to DRB4 alleles, she is correct that the conserved sequence provided would not likely be useful in obtaining a cDNA from which the HLA-DRB4 allele sequences could be established. However, this is

irrelevant in practice because typing is never carried out for the HLA-DRB3, HLA-DRB4 or HLA-DRB5 alleles. These alleles are encoded at loci that distinct from the DRB1 locus and the genes expressed at these loci are minor HLA sequences of no importance in typing. (The gene found at the DRB2 locus is not known to be expressed in any cell - i.e., it is a null locus.) This application thus focuses on only the HLA genes that are expressed at the HLA-DRB1 locus.

CONCLUSION

12. It is my personal belief that the knowledge regarding the history of the identification of HLA genes, it is indisputable that the three polymorphic regions and the conserved region of the HLA-DR-β-A, HLA-DR-β-B, and HLA-DR-β-C alleles, first identified and characterized in the '786 application, served as very important tools for the identification of additional HLA-DR-β chain alleles and probes for hybridization-based HLA-DR typing.

13. I hereby further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing therefrom.



Jack L. Strominger, M.D., D.Sc.

Signed this 16th day of June, 2003

at New York, New York.